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Pain in Parkinson disease: facts and uncertainties

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Abstract

Background: Pain is one of the most common and troublesome non-motor symptoms of Parkinson's disease; it can appear at any time during the disease, and it is often present before diagnosis. However, there is little or no consensus on its definition.

Methods: An expert group of clinicians with relevant research experience met to review the existing evidence, and to identify gaps in our understanding towards an optimized therapy of pain in Parkinson's disease.

Results: Key findings from epidemiologic, neurophysiologic, neuroimaging and clinical studies are reviewed. In each case, the evidence base is limited by wide variations in the definitions of pain applied, study methodologies and populations evaluated.

Conclusions: Disease-related as well as medical conditions trigger spontaneous pain in Parkinson patients which is then abnormally processed and results in painful manifestations in specific body parts. Dopaminergic medications like rotigotine as well as opiate analgesics like oxycodone have shown positive results but future studies with more detailed pain characterization at inclusion are warranted.

Introduction

Although pain has long been acknowledged as a feature of PD [1], it remains an under-diagnosed and under-treated symptom. When present, pain negatively impacts the quality of life [2] and survey's evaluating patient perceptions of their most bothersome symptoms consistently find that pain ranks high in all stages of the disease [3, 4].

A key reason for the lack of recognition and under-treatment is the difficulty in defining and characterizing pain in PD. Different studies have categorized pain in several ways including: PD (including fluctuation-related, dyskinesia-related and central pain) vs. non-PD related pain [5-7]; primary (CNS) vs. secondary (musculoskeletal system) pain [8]; nociceptive vs.

neuropathic, chronic vs. acute, and pain in different body parts [9]. Several experts have tried to better define the clinical features and taxonomy of pain in PD [10,11]. Clinically it is important in PD to distinguish pain arising from dystonic posture (dystonic pain) from pain localized in body parts unaffected by dystonia (non-dystonic pain) and secondary to musculoskeletal, peripheral or central neuropathic pain. [6]

To address this issue, an expert group of clinicians reviewed the existing evidence to identify gaps in our understanding towards an optimized therapy of pain in PD. This article reviews the findings of the main research approaches (epidemiology, neurophysiology, imaging and clinical research) to evaluate what insights they can offer to better define and characterize pain in PD. A full list of references is provided in the supplementary materials.

Epidemiologic research

Studies in PD have consistently shown that pain can appear at any time during the disease [12], often before diagnosis [13] and its prevalence is higher than controls (Table 1) [7,15-20]. Most recently, the validation of the King's Parkinson's disease Pain Scale (KPPS) study showed higher KPPS total score in PD patients versus age and sex matched controls mostly in the domains of musculoskeletal, chronic, fluctuation-related, nocturnal, orofacial, and radicular pain [21].

The wide range of results can largely be explained by the heterogeneity of pain types studied and lack of objective outcome measures. Added to this complexity are the various painful co-morbidities, such as arthritis and muscular-skeletal deformities that often co-exist in elderly PD [20-22]. Patients may also have different combinations of pain types at the same time and the presence of depression (common in PD) is well known to associate with

higher pain sensitivity [7,18]. Indeed, even studies showing no absolute difference in pain prevalence revealed that after adjustments for osteoarticular comorbidity, PD patients are twice as likely to suffer from chronic pain than age-matched non-PD control [7].

They are also more likely to receive prescription of analgesics than the general population (82% vs 77%), including medications for chronic use (33 vs 20%) like opiates, acetaminophen [23].

Neurophysiology

In the last decade, several neurophysiology and neuroimaging studies have provided useful information on nociceptive input processing (*evoked* pain) mechanisms in PD and investigated pain threshold and pain tolerance using different kinds of stimulation (e.g. electrical, thermal, laser stimuli) [24-35], nociceptive withdrawal reflex (NWR) [24,36,37] and scalp laser evoked potentials (LEPs) [29-32, 38]. Pain threshold is defined as the minimum intensity of stimulation at which subjects report a change in sensation from unpainful to faintly painful and evaluates the sensory-discriminative component, while pain tolerance is defined as the minimum intensity of stimulation perceived as an intolerable painful sensation and assesses the affective and cognitive dimension [39-40]. By contrast, the NWR following electrical stimulation of the sural nerve explores pain processing in the spinal cord [41-43] and LEPs recordings are used to non-invasively assess the functional status in some cerebral structures (the cingulate gyrus and insula) responding to nociceptive inputs [44-46].

To date, PD patients have been enrolled under different types of chronic dopaminergic treatment rather than drug naïve (Table 2) and presented a decreased pain threshold/tolerance to various stimuli, a reduced NWR threshold to electrical stimuli and

changes in N2/P2 LEP amplitude [25, 27, 28, 31, 32, 35, 47, 48]. These abnormalities point to increased activity in both the ascending lateral and medial pain pathways [49]. Although peripheral mechanisms may also contribute, and several skin biopsy studies investigating small fibers or terminal endings have documented cutaneous denervation [50-52], recent studies have indicated that their role is not as important as central mechanisms to abnormal pain processing [38]. Indeed, neurophysiologic studies in PD patients with different kinds of pain including muscoloskeletal, peripheral or central neuropathic have shown abnormalities of nociceptive input processing at both spinal and cortical level [31,32].

Moreover, lack of correlation between pain-processing abnormalities and intensity/quality of pain does not support an exclusive relationship. Although some observations suggest that spontaneous pain is associated with additional changes in nociceptive processing mechanisms [Schestatsky et al. 2007; Tinazzi et al. 2010], the majority of the studies indicate that similar changes in central pain processing intervene in patients with PD with and without pain. [29,31,32,35,47].

In summary, in PD disease-related (e.g. motor complications, dystonia, marked rigidity or bradykinesia) as well as medical conditions (e.g. osteoporosis, rheumatic disease) trigger spontaneous pain which is then abnormally processed and results in painful manifestations in specific body parts [53].

Neuroimaging

Functional neuroimaging techniques have contributed to expand our understanding of the neural basis of pain [54]. The consensus is there is no single ‘pain center’ but instead a complex ‘pain matrix’ including (but not limited to): thalamus, amygdala, hypothalamus,

insula, primary and secondary somatosensory cortexes (S1 and S2), primary motor cortex and anterior and posterior cingulate cortexes. The basal ganglia play a crucial link between pain and the emotional experience through what is collectively known as the 'salience network'. The salience network is an intrinsically connected large-scale network anchored in the anterior insula and dorsal anterior cingulate cortex, and includes three key subcortical structures: the amygdala, the ventral striatum, and the substantia nigra/ventral tegmental area [55]. Several studies have shown that chronic pain shifts salience network activity [55,56], while other studies have indicated that in PD activity of the salience network is affected by cognitive and motor dysfunction [57-59].

PD patients tested in the OFF' state, were found to have significantly increased cortical pain-induced activation (characterized by increased regional cerebral blood flow) in the ipsilateral prefrontal cortex, ipsilateral insula, and contralateral anterior cingulate in comparison with the control group [27]. These observations suggest presence of an abnormal pain-induced activation in two main pathways, the sensory discriminative processing (mediated via the insula) and the affective motivational processing (medicated by the anterior cingulate cortex and prefrontal cortex) [27]. In another imaging study by the same group, significant correlations between [123I]-FP-CIT binding to dopamine transporters and subjective heat pain threshold were shown in the posterior cingulate cortex and insula (i.e. extrastriatal areas). By contrast, there was no correlation between striatal dopamine transporter binding and pain threshold - suggesting that pain perception abnormalities in PD may not be directly related with striatal dopaminergic dysfunction but could perhaps reflect extrastriatal dopaminergic dysfunction, with an imbalance between the sensory and the affective cerebral nociceptive pathways [60]. Such findings are supported by another study using multimodal imaging techniques which demonstrated significant thinning in several cortical regions in PD with persistent versus those without pain and highlighted the contribution of frontal, prefrontal and insular areas in nociceptive modulation and accumbens-hippocampus disconnection [61].

In one of the few specific fMRI studies, Tan et al combined resting state and pain-stimuli-induced task state fMRI to identify alterations in functional connectivity related to pain in PD [59]. Compared with controls, PD patients showed decreased functional connectivity in the putamen during evoked pain (51°C heat pain stimuli) as well as decreased functional connectivity in the salience network and the sensorimotor network during the rest state. They found that functional network connectivity between the basal ganglia and the salience network are reduced during both states in PD. In addition, the right frontoparietal network was significantly disturbed during evoked pain [59].

Impact of dopaminergic medication on pain and pain processing mechanisms

Several studies using different methodologies have investigated the influence of dopaminergic medication on pain in PD. As before, these studies have enrolled patients under chronic dopaminergic treatment rather than drug-naive patients, and so comparisons are limited to differences between the ON and OFF states.

While no correlation has been found between spontaneous pain and daily levodopa dose, some studies have reported that pain of variable quality and localization (muscular pain, pain associated with degenerative osteoarticular changes, and oral or genital pain) may fluctuate in intensity during OFF and ON states [62, 63], particularly in presence of dyskinesia [34]. This is supported by several uncontrolled observations, which indicate that spontaneous pain may be minimized by strategies like continuous dopaminergic release and stimulation (e.g. apomorphine/levodopa infusion, and deep brain stimulation) that usually improve levodopa-related motor complications [64-69]. However, owing to the lack of a placebo group these observations need to be considered with caution.

With regards to the impact of levodopa on *evoked* pain, there have been several conflicting studies, possibly due to differences in study designs, patient selection and pain types that had been investigated. Acute levodopa challenges have found either no effect or have shown that levodopa normalizes the decreased pain threshold observed in PD patients [24-27, 30, 65, 70]. In one study, acute levodopa medication in an otherwise chronically treated patient group increased the NWR threshold to electrical stimuli in pain-free PD patients [24], but a later study failed to confirm this finding [25]. These variable results may reflect methodological issues, placebo effect or other confounding factors, including the presence of levodopa-induced motor complications and suggest involvement of neurotransmitter other than the dopaminergic system. For example, when comparing the levodopa-induced change in cold pain threshold and tolerance among stable responders, fluctuators without and with dyskinesia, threshold increase was larger in dyskinetic patients and in fluctuators than in stable patients [34]. However, all previous studies dealing with levodopa-induced changes in pain thresholds failed to specify whether patients were stable levodopa responders, fluctuators, or had dyskinesia. Of note, the studies which did find a significant levodopa effect on pain thresholds typically enrolled patients with a long disease duration and under chronic dopaminergic therapy, and we can therefore assume they included some with motor complications [24-27]. This includes neuroimaging studies showing that levodopa administration increases pain thresholds to cold water test and reduces pain-induced nociceptive cerebral areas activation in both pain-free PD and in PD patients with neuropathic pain [27,28].

Thus, there is evidence that levodopa directly modifies pain thresholds, favoring dopaminergic system involvement. However, neuroimaging studies of acute apomorphine challenges have found that direct dopamine receptor stimulation with apomorphine has no effect on electrical and heat-pain thresholds or as compared with placebo in pain-free PD patients [33]. The differences between the dopamine precursor levodopa and apomorphine

suggest that the impact of levodopa on pain thresholds may, at least in part, be mediated by other monoaminergic systems such as noradrenaline. Indeed, all the key thalamic and midbrain nuclei identified as being involved in the so-called 'pain matrix' [71,72], are directly or indirectly affected in PD implying involvement of non-dopaminergic pathways including noradrenergic and serotonergic transmission.

Clinical trials

There has been a disparate range of poor quality clinical trials evaluating pain in PD, with significant differences in the types of pain considered, and methodologies. Taken collectively, the studies have been underpowered to assess pain, have not used relevant comparator groups and many have been open-label. Lack of homogeneous pain definitions have not only led to important differences in inclusion and exclusion criteria, but also in the pain outcomes measured. Moreover, correct characterization of nociceptive and neuropathic pain is an important basis for treatment decision.

Neurophysiology studies in patients who have undergone DBS have been more consistent than those conducted with levodopa, with most studies showing increased heat pain threshold in PD patients with and without pain [65,68,73]. Subjective improvement in PD-related pain has been documented also after pallidotomy [74,75], and DBS of the globus pallidus [66] and subthalamic nucleus [65,76] in advanced PD, and therefore lend further support to the role of the basal ganglia in modulating pain. Of note, the study by Kim et al [76] asked DBS candidates to rate the severity of their pain in each body part. Of the 23 patients reporting pain, 20 (87%) showed pain improvement after 3 months. Eighteen patients described fluctuation-related pain at baseline, and of these 12 reported a decrease in, and 5 complete disappearance of OFF pain. Of the 4 patients with non-fluctuating preoperative pain, 2 reported improvement, however new pain was reported to develop in many patients during the 3-month follow-up, suggesting that the study captured a mixture of OFF-related pain and other pain types [76].

The idea that PD pain associated with motor fluctuations may be minimized by continuous dopaminergic strategies was first assessed in the RECOVER study, which evaluated non-specified pain as an exploratory outcome in a subpopulation of PD patients who had nocturnal/early morning problems, and reported improvements in pain using a Likert scale with rotigotine compared with placebo [77,78]. More recently, the DOLORES study was the first double-blind placebo-controlled study to investigate the effect of a dopamine agonist (rotigotine) on PD-associated pain [79]. Although the DOLORES study was underpowered to observe statistical differences, it did show a general improvement in PD-associated pain intensity for rotigotine versus placebo (numerical difference of 0.76 Likert points). Unfortunately, because the Likert scale assesses pain severity as a composite of all types of PD pain, it was not possible to determine which pain type drove the improvement. However, the treatment effect appeared to be numerically greater in the subgroup of patients with 'fluctuation-related' pain (1.07 Likert points) [79]. This is in line with the efficacy of rotigotine in managing the symptoms of wearing-off and suggests an indirect effect of pain improvement secondary to motor improvement [36,80].

Other than this, there is scant clinical trial data on the pain response to the other currently available PD medications. An exploratory *post-hoc* analysis analyses of pooled data from safinamide trials has shown significantly reduction in the number of concomitant pain treatments vs. placebo [81]. Another open-label study in 14 patients has reported that continuous levodopa infusion with the levodopa intestinal gel had 'good' effects on severe nocturnal dystonic pain, but the outcome measures used to assess this aspect were not reported [82].

Taking into consideration that not all PD pain may be dopaminergic mediated, one open-label, 6-week study evaluated the efficacy of the serotonin and norepinephrine reuptake inhibitor duloxetine in PD patients with painful phenomena. Thirteen of the 20 PD patients who completed the study reported varying degrees of pain relief, with significant improvements in pain visual analog scales, brief pain inventory (BPI) and the Short-Form McGill Pain Questionnaire. However, there was no change in pain threshold after treatment [83].

Finally, the efficacy and safety of opiate analgesics has been studied in PD patients experiencing chronic pain. These types of study had previously been avoided due to concerns about the use of opiates in PD due to the risk of aggravating constipation as well as inducing somnolence, confusion and worsening cognition. However, the combination of oxycodone with the peripheral opiate antagonist naloxone (in a fixed ratio of 2:1) minimizes the risk of constipation [84] and opens the possibility of using this drug to treat PD pain. In favor of this approach, one small observational study showed significant pain relief as assessed by reductions in numeric rating scales and in BPI scores [85]. Moreover, no significant changes were observed in bowel function and constipation symptoms over the 8-week study period.

To test this approach further, the PANDA study was a large double-blind placebo controlled randomized study which recruited patients with at least one type of severe pain, and an average 24-hour pain score of at least 6 out of 10 (on an 11-point pain scale). Although the primary endpoint (24-hour pain score at week 16) was not significant, assessments of 24-hour pain at other time-points during the study and other secondary endpoints (responder rates for 24-hour pain scores) favored treatment with oxycodone–naloxone [86]. In addition, subgroup analyses demonstrated potential added benefit to patients from severe

musculoskeletal or nocturnal pain types. As the first trial of its kind, the methods in this study were exploratory, and many lessons can be learned. The study was enriched for patients with severe pain, but patients are unlikely to tolerate severe pain for more than a few weeks, which might explain the dropout rate and large number of missing data at 16 weeks and regression to the mean in both the opiate and placebo treatment arms after 16 weeks. The authors of the study also suggested that assessment of change in less severe pain might have better represented the treatment effect. Interestingly the maximum dose allowed in the study was in the low range of that used in chronic pain patients. Given the good safety profile and the limited increased risk of constipation and nausea in the PD cohort treated with active drug, future studies could consider the use of higher doses particularly in younger patients. Another important study limitation was the use of levodopa as rescue medication, which might have confounded assessment on some types of PD-related pain [86]. The study also showed a large placebo response, which is a problem in pain research because expectation and previous experience are both well-established key mediators of both placebo and nocebo effects [87], and indeed for pain itself. Systematic reviews of chronic pain trials have shown that a substantial proportion of the beneficial and adverse effects of a drug is attributable to placebo [88-90].

What next?

Bringing together the various research angles we can conclude that pain is a common feature of PD, and PD patients experience more pain than age-matched controls. Accumulating evidence supports the concept that in PD pain etiology is multifactorial although musculoskeletal pain seems far more frequent than disease-related pain, at least in patients with severe complaints. Specific brain connectivity and structural abnormalities are present in PD patients likely resulting from changes in the processing of central and peripheral nervous system painful stimuli. In specific cases this maybe aggravated by the presence of skeletal deformities and other various co-morbidities a PD patient may also suffer [91].

Considering all the limitations observed in previous clinical trials the need for a widely accepted definition of pain in PD is obvious. Moving forward, it is essential that studies should be adequately powered, recruit patients experiencing the types of pain that can be targeted by the proposed mechanism of action of the intervention and employ relevant controls and outcomes measures [92]. As a construct, pain is difficult to assess – there is no unit for measurement as it is a subjective experience and each person's interpretation of pain will differ based on past experiences and expectations. Use of validated pain scales will aid enrichment of the clinical population for tailored therapy based on the type of PD pain. At present, the KPPS [21] is the only scale validated for use in PD and is now being used by several investigators. The scale is likely to evolve with use, and can be complemented in future trials with other scales.

It will be important to further clarify the role of the dopaminergic system in modulating pain. It may also be interesting to understand why pain is more common in PD, than in atypical parkinsonian disorders like MSA, PSP and corticobasal degeneration [93]. The influence of genetic variants of the COMT enzyme, which are associated with different responses to acute and chronic pain [94,95] also merits further evaluation. Considering non-dopaminergic mechanisms will also be important. For example, the efficacy of certain antidepressants and antiepileptic drugs warrants testing [92]. Likewise, although there has been one small open-label study with duloxetine [83], the influence of the noradrenergic system certainly requires further study. Finally, since use of over the counter non-steroidal analgesics is so high in PD [23], there is an urgent need to evaluate which types of pain (if any) they improve.

Management of pain in clinical practice

From the management perspective, it is currently impossible to give firm advice based on the paucity of compelling evidence. Most neurologists treat patients with chronic pain, but few have received any training in this area, underscoring a clear educational need. Nevertheless, is frequently under-recognized and often not reported by patients, and because it can have such an impact of daily quality of life – it is incumbent on clinicians to investigate about its presence and assess it in relation to the whole spectrum of non-motor symptoms [96,97]. Clinicians should try to understand what type of pain the patient is suffering because the underlying mechanisms and treatment options vary. While fluctuation-related pain may respond to adjustments in dopaminergic therapy or DBS, dystonic pain to botulinum toxin injections and central pain may respond to centrally pain-modulating medications. Certainly, the good response of some pains to dopaminergic medication means that clinicians should ensure that the patients current dopaminergic therapy is optimized [98].

Non-pharmacologic approaches may also be of benefit. The benefits of physiotherapy for pain are increasingly accepted with increasing evidence that physiotherapy consistently reduces self-reported pain in adults suffering from a variety of painful conditions [99]. Musculoskeletal pain in PD often relates to camptocormia and lumbar spine syndromes, similar to the majority of elderly in the general population. All methods (such as physical therapy, warming -up and stretching) used to treat these painful conditions can be applied in PD patients. Other systematic reviews have suggested that patients with chronic pain will benefit from around 150 min of moderate equivalent physical activity per week [100]. It is also important to consider secondary causes of pain – for example painful leg edema may indicate switching antiparkinsonian medication, and abdominal pain could indicate that the patient is suffering from constipation. Comorbidities should be considered, as pain can often

be attributed to a non-PD causes including arthritis, diabetes and cancer. If pain is severe despite optimizing dopaminergic therapy, one can consider therapy with low dosages of prolonged release oxycodone/naloxone [80].

We hope this review draws attention to the limitations of published studies and the difficulties in developing guidelines based on the findings so far. There is an urgent need for consensus on what constitutes PD pain. Clarity in this area will undoubtedly lead to better designed studies.

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Table legends

Table 1: Prevalence of pain estimates from epidemiological studies including a control group

Table 2: Results from neurophysiology studies evaluating pain thresholds in PD patients under OFF conditions.

Table 1

Study	Pain type	PD patients with pain N (%)	Control subjects with pain N (%)	P value
Chaudhuri et al [14]	All pain	27%	30%	0.6
Etchepare et al [15]	Back pain	104 (60%)	100 (23%)	<0.001
Broetz et al [16]	Back pain	101 (74%)	132 (27%)	<0.001
Negre-Page et al [7]	Chronic pain (all types)	450 (61%)	98 (58%)	0.74
Defazio et al [20]	All pain	402 (70%)	317 (63%)	0.04
Beiske et al [17]	All pain	176 (83%)	Norwegian population (30%)	<0.001
Ehrt et al [18]	All pain	227 (67%)	100 (39%)	<0.001
Madden and Hall [19]	Shoulder pain	25 (80%)	25 (40%)	0.006
Chaudhuri et al [21]	Seven types of pain validated in the KPPS	N=178 Mean ±SD KPPS total score: 25.2 ±22.1	N=83 Mean ±SD KPPS total score: 9.34 ±12.5	<0.026

Table 2

Study	PD patients with pain vs. healthy controls	Pain free PD patients vs. healthy controls	PD patients with pain vs. PD patients without pain
Pain threshold to mechanical stimuli			
de Andrade D et al, 2012 [73]	-	Reduced threshold	-
Pain threshold to electrical stimuli			
Gerdelet Mas et al, 2007 [24] (musculoskeletal pain)	-	Reduced threshold	-
Mylius et al, 2009 [26]	Reduced threshold	Reduced threshold	Similarly reduced threshold
Zambito Marsala et al, 201135 (musculoskeletal pain & peripheral neuropathic pain)	Reduced threshold	Reduced threshold	Similarly reduced threshold
Perrotta et al, 2011 [25]	-	Reduced threshold	-
Pain threshold to cold water			
Brefel-Courbon et al, 2005 [27]	-	Reduced threshold	-
Lim et al, 200834	Reduced threshold	-	-
Brefel-Courbon et al, 2013 [28] (primary central pain)	Reduced threshold	Reduced threshold	Similarly reduced threshold
Pain threshold to heat thermode			
Djaldetti et al, 2004 [47] (primary central pain)	Reduced threshold	Reduced threshold	Lower threshold in patients with pain
Schestatsky et al, 2007 [29] (primary central pain)	Reduced threshold	Reduced threshold	Lower threshold in patients with pain
Mylius et al, 2009 [26] (musculoskeletal pain)	Normal threshold	Normal threshold	Similar threshold
Dellapina et al, 2011 [33]	-	-	Similar threshold-
Nandhagopal et al, 2010 [48]	-	Normal threshold	-

Pain threshold to laser CO2			
Schestatsky et al, 2007 [29] (primary central pain)	Reduced threshold	Normal threshold	Lower threshold in patients with pain
Tinazzi et al, 2008 [30]	-	Reduced threshold	-
Tinazzi et al, 2009 [31]	-	Reduced threshold	-
Tinazzi et al, 2010 [32]	-	Reduced threshold	-
Pain threshold to electrical stimuli			
Zambito Marsala et al, 2011 [35] (musculoskeletal pain & peripheral neuropathic pain)	Reduced threshold	Reduced threshold	Similarly reduced threshold
Nociceptive withdrawal reflex threshold			
Gerdelet Mas et al, 2007 [24]	-	Reduced threshold	-
Perrotta et al, 2011 [25]	-	Reduced threshold	-
Mylius et al, 2011 [37] (musculoskeletal pain)	Reduced threshold	-	-
Laser evoked potentials			
Tinazzi et al, 2008/2009/2010 [30-32] (musculoskeletal pain)	Reduced N2/P2 amplitude	Reduced N2/P2 amplitude	Lower N2/P2 amplitude in patients with pain
Schestatsky et al, 2007 [29]	Increased N2/P2 amplitude (primary central pain)	Normal N2/P2 amplitude	Increased N2/P2 amplitude in patients with pain
Zambito Marsala et al, 2017 [38]	-	Reduced N2/P2 amplitude	-